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Protective and therapeutic role of *Itrīfal* (Unani dosage form) in neuro behavior, neurodegeneration, and immunomodulation: An appraisal

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A R T I C L E I N F O

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A B S T R A C T

Background: Itrīfal, an important dosage form of Unani medicine, was introduced some 1000 years ago for the treatment of mainly brain disorders. This semi-solid dosage form is usually prepared by adding the dried fruits of *E. officinalis, T. chebula,* and *T. bellirica*, along with other important herbs mainly of plant origin. The present review is aimed at evaluating the potential effects of different formulations of *Itrīfal* and its important ingredients with respect to traditional uses and scientific studies.

Methods: The present review was carried out after going through Unani classical literature related to the potential therapeutic uses of various formulations of *Itrīfal* in cerebral diseases. The scientific data related to pharmacological activities and biologically active compounds of various formulations of *Itrīfal* and their important ingredients were explored through search engines like PubMed, Science Direct, Springer, MEDLINE, Research Gate, and Google Scholar.

Results: The review of Unani classical literature revealed that various formulations of *Itrīfal* eliminate phlegmatic, bilious, and melancholic morbid humors produced because of *ihtirāq* at the microcellular level in cases of cerebral diseases. The phytochemical review of different ingredients of *Itrīfal* revealed that they contain various bioactive secondary metabolites, including flavonoids, polyphenols, monoterpenes, alkaloids, glycosides, amino acids, tannins, etc., which possess several pharmacological activities, such as antioxidant, neuroprotective, anxiolytic, antidepressant, anti-aging, memory enhancer, neuroprotective, immunomodulatory, etc., through different mechanisms of actions like inhibition of acetylcholinesterase and butrylcholinesterase enzymes, modulation of neurotransmitters, interaction with adrenergic, dopaminergic, and serotonergic systems, blockade of dopamine receptors and enhancement of GABAergic neurotransmission, neurogenesis, synaptogenesis, etc.

Conclusion: Itrīfal has been prepared by adding rationale mixtures of herbs, which possess preventive and curative effects in brain diseases. They can provide much-needed protection to the brain and nerves against oxidative stress and other disease-oriented factors. The limitations with this unique dosage form of Unani medicine are that adequate scientific studies have not been carried out on different preparations of *Itrīfal* for holistic and scientific exploration of such an extraordinary dosage form. Hence, it is suggested that more studies on different aspects, like pharmacological, toxicological, pharmacodynamics, pharmacokinetics, etc., may be carried out in the future.

Abbreviations: ABTS, 2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid; AchE, Acetylcholinesterase; BDNF, Brain-derived neurotrophic factor; CAT, Choline acetyltransferase; CCl4, Carbon Tetrachloride; CNS, Central Nervous System; CREB, cAMP-response element binding protein; DA, Dopamine; DNA, deoxyribonucleic acid; DPPH, 2, 2-Diphenyl-1-picrylhydrazyl; FSH, Follicle Stimulating Hormone; GABA, Gamma-aminobutyric acid; GSH, Glutathione; IFN, Interferons; IL, interleukin; LH, Luteinizing Hormone; MAO, Monoamine oxidase inhibitors; MDA, Malondialdehyde; MPP-2, Matrix Metalloproteinase-2; NE, Nor-Adrenaline; NO, Nitric Oxide; PC, Pheochromocytoma; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator PGC-1alpha; ROS, Reactive Oxygen Species; SDG, Secoisolariciresinol diglucoside; SOD, Superoxide dismutase; STZ, Streptozotocin; TNF, Tumour Necrosis Factor; VEGF, Vascular Endothelial Growth Factor.

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1. Introduction

The Unani system of medicine, which is also referred to as Greco-Arab medicine, has been practiced mainly by following the fundamentals of the Hippocratic doctrine of humoral theory since ancient times (Kausar et al., 2021). In Unani medicine, the concept of compounding drugs was postulated by Galen (131 c.–201 AD), who is regarded as the father of polyherbo-mineral mixtures (Ansari et al., 2019). Approximately 90 dosage forms including solid, semisolid, liquid, and gaseous in nature, are described in Unani classical literature (Ansari et al., 2016). Certain dosage forms are specifically prepared for the prevention and treatment of the diseases in particular systems. For instance, *Bāsalīqūn* (fine powder) for eye diseases, *Tiryāq* (antidote) for poisoning, *Jawārish* (semisolid preparation) for gastrointestinal disorders, *Khamīra* (semisolid preparation) for cardiac diseases, *Zar'ūnī* (semisolid preparation) for renal diseases, *La'ūq* (linctus) for respiratory diseases, *Mufarrih* (semisolid preparation) for cerebral and cardiovascular disorders, *Yāqūtī* (semisolid preparation) for cardiac ailments, *Labūb* (semisolid preparation) for sexual dysfunctions (Anonymous, 2012), and *Itrīfal* (semisolid preparation) for the diseases of brain and stomach (Kabeeruddin, 2010). *Itrīfal* is a dosage form whose main ingredients are three botanical drugs such as *Âmla* (*Emblica officinalis* Gaertn.), *Halela* (*Terminalia chebula* Retz.), and *Balela* (*Terminalia bellirica*Roxb.) (Anonymous, 2012).These three ingredients are called '*triphalā*'(Sanskrit: *tri*= three and *phala*= fruits), from which *Itrīfal* is derived. It is prepared in the form of a confection by adding honey or sugar (Kabeeruddin, 2010). Unani physicians advised that *Itrīfal* should be used after two months of its preparation for better therapeutic efficacy (Hafeez, 2005).It is believed that certain biologically active compounds are formed during this period. It is also advised that the formulation of *Itrīfal* should not be used for a long duration since it causes weakness of the stomach (Hafeez, 2005). The same preparation containing chiefly *Emblica officinalis*, *Terminalia chebula*, and *Terminalia bellirica*, usually in the same ratio, has been used by the name of *Triphalā*' in Ayurveda since more than 1000 years as evident in Ayurvedic literature, mainly *Charakā Samhītā* and *Sushrūtā Samhītā*. In Ayurvedic knowledge, these three plant-origin drugs are known as *tridoshic rasāyānā* (a therapeutic agent responsible for maintaining the equilibrium of three humours), which is believed to augment longevity and revitalization in all age groups(Peterson et al., 2017). The distinguished feature of *Itrīfal* from *Triphalā*' used in Ayurvedic medicine is that in Unani medicine, *Itrīfal* is used only in the semisolid form, which contains sugar or honey (Khan, 1995; Hafeez, 2005; Kabeeruddin, 2010), whereas in Ayurveda, *Triphalā*' is mostly used in the powder form, and sometimes the powder of *Triphalā*'is advised to take along with honey or sugar (Peterson et al., 2017).

Classical literature and pharmacopoeias of Unani medicine describe several formulations of *Itrīfal*, which are prescribed for the treatment of various ailments related to brain, nerves, stomach, intestine, rectum, skin, lymphatic glands (Jurjani, 2010), cognitive behavior, oral cavity, lungs, etc (Al-Haruni, 2018). In the present scientific era, studies have confirmed that certain formulations like *Itrīfal Aftīmūn* (Gupta et al., 2022), *Itrīfal Muqawwī Dimāgh* (Siddique et al., 2021), *Itrīfal Saghīr* (Kamali et al., 2012), *Itrīfal Shāhtra* (Khatoon et al., 2022), *Itrīfal Ustūkhuddūs* (Hussain et al., 2003), *Itrīfal Kishnīzī* (Koneru et al., 2010; Koneru et al., 2011), and *Itrīfal Hakim Ali* (Ismail et al., 2022) are potentially useful in the treatment of various diseases. *Itrīfal Kishnīzī* showed significant antidepressant potential against the Despair Swim Test and Tail Suspension Test in mice and antioxidant effects against the DPPH model in a dose dependent manner (Koneru et al., 2010, 2011). *Itrīfal Muqawwī Dimāgh* has been reported to significantly reduce oxidative stress and increase antioxidant enzymes and tyrosine hydroxylase activity in the transgenic Drosophila model of Parkinson's disease (Siddique et al., 2021). Other studies reveal that three myrobalan fruits of *Itrīfal* significantly possess immunomodulatory, antioxidant, antidiabetic, anticancer, antimicrobial, cardioprotective, radioprotective, wound healing, and anticataract effects. The micronutrients and biologically active compounds present in such herbs modulate the immune system and prepare the body against any disease. Studies have proven that such defense mechanisms protect many neurological diseases, such as Parkinson's disease, Alzheimer's disease, convulsions, anxiety, and dementia. Polyphenols, mainly chebulic acid, present in the myrobalan fruits prevent oxidative stress. Other phytoconstituents like flavonoids, gallic acid, ellagic acid, and tannins have immunostimulatory and immunosuppressant properties. It has also been proven that the bioactive constituents present in the myrobalan fruits significantly remove reactive oxygen species from HeLa cells. A clinical study revealed that mental concentration and sleep are promisingly improved after regular use of *Triphala Churna* (Ayurvedic formulation) (Ahmed et al., 2021).

The Unani system of medicine has been recognized as one of the indigenous systems of Indian medicine and has been integrated into the national health care delivery system by the Indian government. This traditional system has also become part of the mainstream system of medicine in other countries like Iran, Pakistan, Bangladesh, etc. due to its increasing use and scientific research (Khan et al., 2022). The root of Unani medicine has spread throughout the world. A memorandum of understanding has been signed between the Ministry of Ayush, Government of India, and the Department of Pharmacognosy, University of Mississippi, United States of America for evaluation of the therapeutic efficacy of Indian medicinal plants. Around 13,000 Indian medicinal plants have been evaluated under this collaborative project in the past five years. The Global Unani Medicine and Research Foundation (GUMRF) has been encompassed under the law of the United States of America. The main objective of GUMRF is to bring forth the researchers of Unani medicine for carrying out scientific research (Viquar et al., 2021). The World Health Organization (WHO) published a benchmark for the practice of Unani medicine, which aims to ensure qualified practice and assure patient safety (Anonymous, 2022a). Likewise, the WHO has also published a benchmark document for training in Unani medicine (Anonymous, 2022b).

The current development in the field of drug discovery and progressive efforts for the exploration of new chemical entities from herbal products have exaggerated the attempts for searching leads (Biradar et al., 2007) from traditional medical systems, including Unani. The present review is aimed at exploring the wisdom for the use of such a unique dosage form of Unani medicine, *Itrīfal*, and the therapeutic potential of different formulations of *Itrīfal* in various diseases, particularly neurodegenerative and other conditions of the nervous system, with respect to traditional and modern scientific knowledge.

2. Materials and methods

The depth of knowledge of *Itrīfal*, its various formulations, origin, wisdom for the preparation of *Itrīfal*, therapeutic properties, etc., was collected through an extensive review of Unani classical and authoritative literature, including *Al-Qanūnfi'l Tib* (The Canon of Medicine) of Ibn Sinā (980–1037 AD), *Zakhīrā Khawārizam Shahi* of Ahmad al-Hasan al-Jurjani (1040–1136 AD), *Kitab al-Mukhtarātfi'l Tib* of Ibn Hubal Baghdadi (1121–1213 AD), *Kitab al-Kuliyāt* of Ibn Rushd (1126–1198 AD), Minhaj *[*[__]]#257;aj al-Dukkān va Dastūr al-Aayān of Abul Mana ibn Abi Nasr Attar Israil Haruni (13th century), *Qarābādīn-i-Kabīr* of Syed Mohammad Husain, *'Ilāj al-Amraz* of Mohammad Shareef Khan (1722–1807 AD*), Qarābādīn-i-Azam va Akmal* of Mohammad Azam Khan (1815–1902 AD), *Qarābādīn-i-Qadri* of Mohammad Akbar Arzani (d. 1722 AD), *Qarābādīn-i-Jalali* of Jalal-ud-Din Amrohī, *Qarābādīn-i-Najmul Ghani* of Najmul Ghani (b. 1859 AD), *Qarābādīn-i-Ehsani* of Ehsan Ali, *Bayaz-i-Kabīr* and *Al-Qarābādīn* of Mohammad Kabiruddin (1889–1976 AD), *Mujarrībāt-i-Razaī* of Syed Raza Hasan Jafri, *Qarābādīn-i-Jadīd* of Abdul Hafeez, National Formulary of Unani Medicine, and The Unani Pharmacopoeia of India (official publication of Government of India). Moreover, the scientific data related to pharmacological activities and biologically active compounds of various

formulations of *Itrīfal* and their important ingredients were explored through search engines like PubMed, Science Direct, Springer, MEDLINE, Research Gate, and Google Scholar. The keywords preferred for the compilation of this manuscript were *Itrīfal*, *Triphalā*', phytoconstituents present in *Triphalā*' and other ingredients, neuroprotective, immunomodulatory, sedative, antioxidant, anti-inflammatory, memory-enhancing, anxiolytic, antidepressant, anti-Parkinson's disease, anti-Alzheimer's disease, etc. properties of different preparations of *Itrīfal* and their individual ingredients.

3. Results

3.1. Historical perspective of Itrīfal

The exact time for the discovery of this dosage form is not mentioned in Unani classical literature, but it is evident that some renowned ancient Unani scholars and physicians, including Ibn Sina (980–1037 AD), depicted certain formulations of this dosage form in his world-famous compendium, '*Al-Qanūn fi'l Tib*'. Two formulations of *Itrīfal Kabīr* and one formulation of *Itrīfal Saghir* are described in this classical text, which he advised to use for the treatment of stomach, intestine, urinary bladder, and sexual disorders (Sina, 2010). Ahmad al-Hasan al-Jurjani (1040–1136 AD) has described a separate chapter of *Itrīfalat* in *Zakhīrā Khawārizam Shahi*, in which formulations of *Itrīfal Kabīr*, *Itrīfal Saghīr*, *Itrīfal Aftīmūni*, *Itrīfal Ghudūdi*, *Itrīfal Muqīl*, *Itrīfal Shahatra*, etc. are advised to use for the treatment of several ailments related to stomach, intestine, brain, skin, lymph nodes, rectum, blood, etc (Jurjani, 2010). Another ancient Unani physician of the 13th century, Abul Mana ibn Abi Nasr Attar Israili al-Haruni, has described two formulations of *Itrīfal* in his famous compendium, '*Minhāj al-Dukkān va Dastūr al-Aayān*', for the treatment of cerebral, psychic, stomach, oral, and respiratory diseases (Al-Haruni, 2018). Such evidence confirms that this important dosage form has been used since olden days in the Unani system of medicine. The classical Unani texts compiled by noteworthy Indian Unani physicians like *Qarābādīn-i-Qadrī* of Hakim Mohammad Akbar Arzani (d. 1722 AD) (Arzani, 2009), *Elaj al-Amraz* of Hakim Mohammad Sharif Khan (1722–1807 AD) (Khan, 2005 a), *Qarābādīn-i-Azam va Akmal* of Hakim Mohammad Azam Khan (1815–1902) (Khan, 2005b), *Qarābādīn-i-Jalali* of Hakim Jalaluddin Amrohi, *Qarābādīn-i-Ehsani* of Hakim Ehsan Ali(Ali, 2006), *Qarābādīn-i-Jadīd* of Hakim Abdul Hafeez (Hafeez, 2005), *Bayaz-i-Kabir* and *Al-Qarābādīn* of Mohammad Kabiruddin (1889–1976 AD) (Kabeeruddin, 2010, 2006) have described many formulations of *Itrīfal* by different names important ones are *Itrīfal Ustukhuddus*, *Itrīfal Kishnīzī*, *Itrīfal Zamanī*, *Itrīfal Sanaī*, *Itrīfal Aftimunī*, *Itrīfal Shahatrā*, *Itrīfal Fauladī*, *Itrīfal Deedan*, *Itrīfal Mulayyan*, *Itrīfal Muqawwī Dimagh*, *Itrīfal Kishmishi*, *Itrīfal Mushil*, *Itrīfal Badiyan*, *Itrīfal Kabīr*, *Itrīfal Irq-i-Madni*, etc., which are used for the treatment of different bodily ailments.

3.2. Wisdom for the preparation ofItrīfal

According to Unani medicine, the development of pathological conditions is based on humoural theory. The human body is composed of four humors or fluids i.e., *dam* (blood or red colored fluids), *balgham* (phlegm or white colored fluids), *safra'* (yellow bile/ yellow- or orange-colored fluids), and *sawda'* (black bile/ black, brown- or blue-coloured fluids). The health of an individual is maintained with the right proportion in the quality and quantity of these humours as per the needs of the body, whereas their inappropriate proportion or any alterations in them are responsible for the development of diseases. Unwanted combustion (*ihtirāq*) in any humors has been correlated with oxidative stress, which is responsible for altering the equilibrium of a particular humour. After *ihtirāq*, all types of normal humours, including *dam*, *balgham*, *safra*', and *sawda'*, produce an abnormal form of *sawda*', which is associated with them and causes many diseases. The Unani physicians believe that an unwanted combustion in the yellow bile is the most dangerous type among all and produces neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, etc. The oxidized form of *sawda'* (black bile) is responsible for developing certain psychiatric and other disorders, including depression, melancholia, insomnia, cancers, indigestion, etc. From the above description, it is clear that an abnormal form of *sawda'* (black bile) produced as a result of oxidative stress, is accountable for several pathological conditions (Kausar, et al., 2021). The Unani physicians advised using preparations of *Itrīfal* for evacuating diseased substances from the brain and stomach (Hafeez, 2005). After going through the ingredients of several formulations of *Itrīfal*, it was found that they contained *Emblica officinalis* Gaertn., *Terminalia chebula* Retz., *Terminalia bellirica* Roxb., *Lavandula stoechas* L., *Cuscuta reflexa* Roxb., *Polypodium vulgare* L., *Operculina turpethum* (L.) Silva Manso., *Convolvulus scammonia* L., *Agaricus albus* L., *Valeriana jatamansi* Jones ex Roxb., *Rosa damascena*Mill., etc (Anonymous., 2006). These individual herbs are supposed to eliminate all types of altered humor, especially *sawda'* (black bile), from the body and are used mainly in the treatment of cerebral and stomach disorders. Studies revealed that the chief ingredients of *Itrīfal*, namely *Emblica officinalis*, *Terminalia chebula*, and *Terminalia bellirica*, possess various pharmacological profiles, including antioxidant, immunomodulatory, anti-inflammatory, radioprotective, hypolipidemic, antidepressant, antihypertensive, antithrombotic, hepatoprotective, anti-aging, cardioprotective, retinoprotective activities, etc(Ahmed et al., 2021). Such studies validated the traditional use of different preparations of *Itrīfal*. These scientific studies also showed the wisdom of ancient Unani physicians for the logical invention of this unique dosage form some 1000 years ago with multidimensional therapeutic values.

3.3. Method of preparation of Itrīfal

All the dried herbs are first cleaned and powdered. The powder of *Triphalā*' (*Emblica officinalis*, *Terminalia chebula*, and *Terminalia bellirica*) is rubbed with almond oil or ghee. All the powdered drugs are then sieved through sieve (80 no.) to obtain the uniform size of all particles. Thereafter, all the powdered drugs are uniformly mixed. The *qiwām* (base) is prepared by adding water and sugar or honey. When the base is prepared, the powder is gradually added to it with stirring. After cooling, the finished product is stored in an airtight jar (Anonymous., 2006 a).

3.4. Commonly used Itrīfal in brain diseases

After going through, classical Unani literature and Unani pharmacopoeias, 15 commonly used preparations of *Itrīfal* in the treatment of cerebral, neurological, and psychiatric diseases were selected. Unani physicians prescribe these preparations in the treatment of cerebral weakness, dementia, melancholia, epilepsy, insanity, psychosis, headache, paralysis, chronic rhino-sinusitis, etc (Anonymous., 2006a, 2006b, 2007, 2008; Kabeeruddin, 2006). (Table 1) The commonly used ingredients in these formulations have been selected based on the presence of such ingredients in a minimum of three preparations mentioned in this manuscript. These ingredients are *Amla* (*Emblica officinalis*), *Halelā Sīyāh* (*Terminalia chebula* (dried immature fruit of black color), *Halelā Zard* (*Terminalia chebula* (dried mature fruit of yellow color), *Halelā Kablī* (*Terminalia chebula*(dried half-mature fruit of brown color), *Balelā* (*Terminalia bellirica*), *Ustukhūddūs* (*Lavandula stoechas*), *Aftīmūn* (*Cuscuta reflexa*), *Gul-i-Surkh* (*Rosa damscena* flowers), *Kishnīz Khusk* (*Coriandrum sativum* seeds), *Gul-i-Banafshā* (*Viola odorata* flowers), *Bisfayij* (*Polypodium vulgare*), etc. (Anonymous., 2006a, 2006b, 2007, 2008; Kabeeruddin, 2006).

3.5. Etiopathogenesis of cerebral, neurological and psychiatric diseases

According to Unani theory, three types of basic impairments, such as *tashvīsh-i-af'āl* (disturbance in functions), *nuqsān-i-af'āl* (partial loss of

Table 1
Commonly used preparations of *Itrīfal*.

Itrifal	Ingredients	Dose	Traditional uses	Scientific studies
Itrīfal Ustukhuddus	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Rosa damscena, Lavandula stoechas, Polypodium vulgare, Cuscuta reflexa, Vitis vinifera*	5–10 g	Headache, paralysis, epilepsy, chronic rhino-sinusitis (Anonymous., 2006 a)	Anti-rhinosinusitis (Hussain et al., 2003)
Itrīfal Saghīr	*Terminalia chebula, Terminalia bellirica, Emblica officinalis*	10–15 g	Cerebral weakness, dementia, haemorrhoids (Anonymous., 2006 a)	Anti-obesity (Kamali et al., 2012)
Itrīfal Kishnīzī	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Coriandrum sativum*	10–30 g	Headache, conjunctivitis, chronic rhino-sinusitis, otalgia, flatulence, haemorrhoids (Anonymous., 2006 a)	Antidepressant (Koneru et al., 2010), antioxidant (Koneru et al., 2011)
Itrīfal Kabīr	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Tanacetum umbelliferum, Myristica fragrans* aril, *Plumbago zeylanica, Pastinaca secacul, Cheiranthus cheiri, Matthiola incana, Wrightia tinctoria, Centaurea behen, Salvia haemotodes*	5–10 g	Cerebral weakness, chronic rhino-sinusitis (Anonymous., 2006 a)	————
Itrīfal Zamani	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Viola odorata, Convulvulus scammonia, Operculina terpethum, Coriandrum sativum, Rosa damscena, Bambusa arundinacea, Nymphaea alba, Santalum album, Cochlospermum religiosum, Ziziphus jujuba, Cordia myxa*	5–10 g	Melancholia, headache, chronic rhino-sinusitis, constipation (Anonymous., 2006 a)	————
Itrīfal Afūmūn	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Operculina terpethum, Cuscuta reflexa, Cassia senna, Plumbago zeylanica, Polypodium vulgare, Lavandula stoechas, Rosa damscena, Pimpinella anisum*	10 g	Melancholia, insanity, psychosis (Anonymous., 2007)	Antitumour (Gupta et al., 2022)
Itrīfal Kishmishī	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Coriandrum sativum, Vitis vinifera*	10 g	Cerebral weakness (Anonymous., 2007)	————
Itrīfal Sanā	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Cassia senna, Fumaria officinalis, Rosa damscena, Viola odorata, Cichoriumintybus*		Cerebral weakness, melancholia (Anonymous., 2007)	————
Itrīfal Zabīb	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Lavandula stoechas, Paeonia emodi, Anacyclus pyrethrum, Vitis vinifera*	10–15 g	Epilepsy (Anonymous., 2007)	————
Itrīfal Muqawwī Dimāgh	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Coriandrum sativum, Amygdalus communis,* poppy seed, *Lactuca sativa, Cinnamomum zeylanicum, Viola odorata, Foeniculum vulgare, Glycyrrhiza glabra, Ziziphus zujuba, Cordia myxa, Lavandula stoechas, Aquilaria agallocha, Hyssopus officinalis, Valeriana jatamansi, Adiantum capillus-veneris, Ficus carica, Vitis vinifera*	5–10 g	Cerebral weakness, chronic rhino-sinusitis (Anonymous, 2006b)	————
Itrīfal Muqawwī Dimāgh	*Terminalia chebula, Terminalia bellirica, Emblica officinalis,* poppy seed, *Althaea officinalis, Rosa damscena, Coriandrum sativum, Amygdalus communis*	10 g	Cerebral weakness, chronic rhino-sinusitis, headache Anonymous., (2008))	Anti-Parkinson's disease (Siddique et al., 2021)
Itrīfal Mulayyin	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Foeniculum vulgare, Operculina turpethum, Rheum emodi, Convulvulus scammonia, Cassia senna, Pistacia lentiscus*	10 g	Headache, chronic rhino-sinusitis, constipation Anonymous., (2008))	Antimicrobial (Devi et al., 2011)
Itrīfal Sanāī	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Cassia senna, Coriandrum sativum,Pistacia lentiscus, Bombyx mori, Fumaria officinalis, Lapis lazuli, Borago officinalis, Melissa officinalis, Lavandula stoechas, Polypodium vulgare*	7–12 g	Headache, cerebral weakness, melancholia, psychosis (Kabeeruddin, 2006)	————
Itrīfal M'āmūl	*Terminalia chebula, Terminalia bellirica, Emblica officinalis, Cinnamomum zeylanicum, Fumaria officinalis, Elettaria cardamomum, Cinnamomum tamala, Pistacia lentiscus, Rosa damscena, Glycyrrhiza glabra, Operculina terpethum,*	12–24 g	Psychosis, cerebral diseases, chronic rhino-sinusitis(Kabeeruddin, 2006)	————
Itrīfal Hakim Alwi Khani	*Terminalia chebula, Terminalia bellirica, Lavandula stoechas,Cuscuta reflexa, Borago officinalis, Santalum album, Polypodium vulgare, Bambusa arundinacea, Paeonia emodi,Lapis lazuli, Rosa damascena, Cichorium intybus, Coriandrum sativum, Solanum nigrum, Viola odorata, Fumaria officinalis, Ziziphus jujuba, Tephrosia purpurea, Vitis vinifera*	9–25 g	Cerebral weakness, vertigo, melancholia, epilepsy, chronic rhino-sinusitis (Ghani, 2019)	————

functions), and *butlān-i-af'āl* (complete loss of functions) are developed in cerebral, neurological, and psychiatric diseases. The later two impairments are caused by excessive morbid humors of cold and wet nature, resulting in obstruction, which further causes disturbance in the impulse generation of all types of nerves. It is further mentioned that the functions of neurons and the brain are either partially or completely hampered due to the accumulation of excessive morbid humors of wet nature, which can be correlated with congestion in the cerebrovascular system and cause either complete or partial paralysis. The homeostasis of the cold and wet nature of humors is responsible for good sleep in the human being. When the equilibrium of these types of humors is disturbed and dryness develops in the brain tissues, it causes insomnia like old age (Sina, 2010). As per Unani fundamentals, the human body is composed of four types of humors, such as *dam* (blood), *balgham* (phlegm), *safrā* (yellow bile), and *sawdā* (black bile). The right proportion in terms of quality and quantity of these humors is responsible for the healthy condition of an individual, whereas an imbalance that occurs in these humors is responsible for the development of a disease. Another important constituent called *harārat-i-gharīziyya* (innate heat) of the body, which is also correlated with BMR, is responsible for maintaining all the vital functions. In contrast to *harārat-i-gharīziyya*, another term *harārat-i-gharība* (unnatural heat), is also mentioned in Unani literature. The deteriorating phenomenon that alters the normal humoral set-up at the cellular level due to the production of unnatural heat is termed *ihtirāq* (unwanted combustion). The production of unnatural heat causes unwanted combustion in all four types of bodily humors, including blood, phlegm, yellow bile, and black bile. Most of the cerebral and psychiatric diseases, including Alzheimer's disease,

Parkinson's disease, dementia, depression (Kausar et al., 2021), melancholia, mixed anxiety depressive disorders, etc., are caused by overproduction of the black bile, which is produced either due to combustion of blood or phlegm, yellow bile, or black bile itself (Sina, 2010; Kausar et al., 2021). Several studies revealed that oxidative stress and excessive free radicals play a major role in the development of various pathological conditions related to the brain, nerves, kidneys, pancreas, joints, and other organs. Moreover, in the present scientific era, oxidative stress and excessive production of reactive oxygen species are considered to be major contributing factors in the development of various bodily ailments. The Unani theory of *ihtirāq* (unwanted combustion) in humors at the molecular level is the same as the modern theory of oxidative stress in terms of the development of diseases (Kausar et al., 2021) (Fig. 1).

3.6. Secondary metabolites in the ingredients of Itrīfal

The three myrobalan fruits namely *Emblica officinalis*, *Terminalia chebula*, and *Terminalia bellirica* are the main ingredients of *Itrīfal* (Anonymous., 2006a, 2006b, 2007, 2008; Kabeeruddin, 2006). The phytochemical analysis has confirmed that these plant-derived drugs yield many phytoconstituents, including alkaloids, phenolic acids, tannins, flavonoids, polyphenols, sterols, saponins, aromatic acids, amino acids, fatty acids, carbohydrates, etc. The isolated biologically active compounds are chebulic acid, chebulinic acid, gallic acid, quinic acid, teresautalic acid, corilagin, methyl gallate, ethyl gallate, quercetin, luteolin, etc (Ahmed et al., 2021). A quantitative phytochemical report revealed that a formulation containing these three fruits possesses tannins (35 %), phenolic compounds (25–38 %), chebulagic acid (5 %), chebulinic acid (5 %), gallic acid (3–7 %), ellagic acid (2 %), and ascorbic acid (0.050–0.33 %) (Sharma et al., 2014).The GC-MS report of the methanolic extract of the three myrobalan fruits revealed the occurrence of ten important biologically active fractions like 1,2,3-benzenetriol, 2-furancarboxaldehyde, 5-(hydroxymethyl)-, 4 H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-, Furfural, 2 H-pyran-2,6 (3 H)-dione, D-allose, n-hexadecanoic acid, DL-proline, 5-oxo-, methyl ester, and undecanol-5, 9-phenanthrene (Amala and Jeyaraj, 2014). One more report showed that these herbs contain a few more important bioactive constituents like oleic acid, a-Sitosterol, 1 H-2, 8a-methanocyclopenta[*a*]cyclopropa[*e*]cyclodecen-11-one, and 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl) hexa-1, 3, 5–1-monolinoleoylglycerol trimethylsilyl ether (Muthiah et al., 2017). The dried fruit of *Emblica officinalis* has been reported to have important tannins like Emblicanin A and B and Punigluconin and flavonoids like kaempferol-3-O-alpha-L- (6 -methyl) amnopyranoside. The important tannins isolated from the dried fruit of *Terminalia chebula* are chebulic acid, gallic acid, ellagic acid, punicalagin, and neochebulinic acid, whereas *Terminalia bellirica* yields methyl gallate, ellagic acid, and gallic acid (Singh and Kumar, 2013).The volatile oil obtained from *Lavandula stoechas* has been reported to contain 42 phytoconstituents, including major ones: pulegone (40.37 %), fenchone (38.85 %), menthol (18 %), menthone (12.57 %), eucalyptol (3.9 %), β -pinene (3.2), 2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde (3.2 %), and β -terpineol (2.3 %) (Goren et al., 2002). The noteworthy constituents isolated from the essential oil of *Lavandula stoechas* are linalool, 1,8-cineole, linalyl acetate, terpinene-4-ol, β-ovimene, and camphor (Cavanagh and Wilkinson, 2002). *Cuscuta reflexa* contains coumarines, flavonoids, triterpenoids, cardiac glycosides, phenylpropanoids, etc. The NMR data of an ethanolic extract of *Cuscuta reflexa* exhibited three new and 12 known constituents, such as 2*H*-pyran-2-one glucosides, cuscutarosides A (1) and B (2), and one new steroidal glucoside, 7*β*-methoxy-*β*-sitosterol 3-*O*-*β*-glucopyranoside. The known phytoconstituents are cuscutaroside A, cuscutaroside B (Tin Thu, et al., 2020), cuscutin, β-sitosterol, amarbelin, kaempferol, stigmasterol, quercetin, myricetin, dulcitol, oleanolic acid, coumarin, etc (Patel et al., 2012). Another important ingredient of *Itrīfal*, *Rosa damascene* contained quercetin, kaempferol, gallic acid, protocatechuic acid, pyrogallic acid, 2-phenylethyl 3,4,5-trihydroxybenzoate, methyl gallate, p-hydroxybenzoic acid, p-hydroxyphenethyl alcohol, astragalin (Wen-ya et al., 2020), anthocyanins, glycosides, flavonoids, terpenes, myrcene, vitamin C, geraniol, nerol, carboxylic acid, etc., among them kaempferol and nerol are the major bioactive compounds. The flavouring agents, include b-ionone, b-damascenone, and d-damascone have also been isolated from the essential oil of rose flowers. Aliphatic compounds, alkaloids, a-cadinol, a-selinene, a-santalene, b-bisabool, b-citronellol, b-linalool, b-selinene, c-cadine, cadinene, citronellol, docosane, elemol, elemene, etc. were also isolated from *Rosa damascena* (Akram et al., 2019). The dried seeds of *Coriandrum sativum*are also added to many formulations of *Itrīfal*. The seeds contain linalool, tocopherol, tocotrienol, β-sitosterol, stigmasterol, polyphenols, include phenolcarboxylic acids (gallic acids, salicylic acids, ferulic acid, caffeic acid), coumarins (scopoletin, umbelliferone, esculin, 4-hydroxycoumarin, esculetin), and flavonoids (rutin, luteolin, hyperoside, hesperidin, diosmin, vicenin, orientine, apigenin, catechin, dihydroquercetin). The methanolic extract has been reported to have 1, 6-octadien-3-ol, 3,7-dimethyl; 1,6-octadien-3-ol, 3,7-dimethyl, 2-aminobenzoate; bicycle[2.2.1]heptan-2-one,1,7,7-trimethyl.; geranyl vinyl ether; 9,10-secocholesta-5,7,10(19)-triene-3,24, 25-triol.; ascorbic acid 2,6-dihexadecanoate, and 7aH-cyclopenta[*a*] cyclopropa[*f*] cycloundecene. Two new aliphaticδ-lactones such as 2α-n-heptatriacont-(*Z*)-3-en-1,5-olide (coriander lactone) and 2α-n-tetracont-(*Z*, *Z*)-3,26-dien-18α-ol-1,5-olide (hydroxy coriander lactone) have also been identified in the methanolic extract of coriander fruits (Jing-Na et al., 2019). Another commonly used ingredient of *Itrīfal*, *Viola odorata* flowers have been revealed to contain flavonoids (quercetin, kaempferol), coumarins (methyl salicylate, caffeic acid), glycosides (rutin), and terpenoids (stigma sterol) (Ali et al., 2023). The volatile oil of sweet violet yields violine, monoterpenes, sesquiterpene phenylbutanone, benzyl alcohol, linalool, α-cardinol, viridiflorol, and globulol (Feyzabadi et al., 2017). The methanolic extract of *Polypodium vulgare* exhibited major phenolic compounds (3-O-caffeoylquinic acid, shikimic

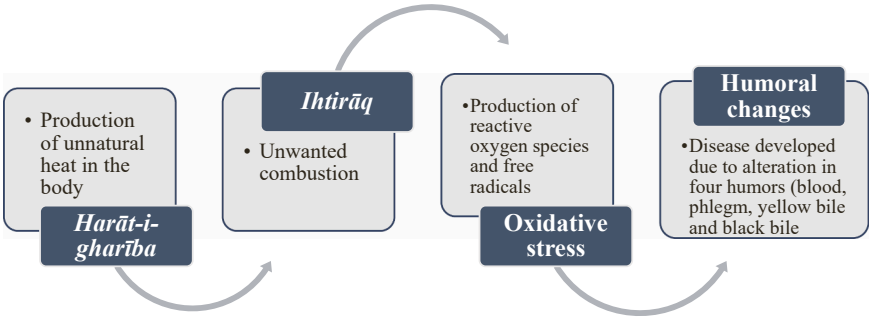

Fig. 1. Pattern of the development of cerebral and psychiatric diseases based on the Unani theory.

acid, catechin, epicatechin), flavonoids (rutin), gallic acid, 5-O-caffeoylquinic acid, hyperoside, and 3,5-di-Ocaffeoylquinicacid (Farras et al., 2021). Its rhizomes yield saponin, glycosides, polypodosapogenin, and phloroglucin derivatives (Khare, 2007). The reported pharmacological activities of various bioactive constituents of different ingredients of *Itrīfal* are depicted in Table 2and Fig. 2.

3.7. Neuroprotective, immune regulation, and other pharmacological effects of Itrīfal (Unani dosage form)

The oxidative stress caused by chemicals like hydrogen peroxide and acrylamide is associated with several neurological disorders. *Itrīfal* or *Triphala*, an imperative dosage form, is used as antioxidant, antihistaminic, anti-inflammatory, and anticancer. A study has reported that *Triphala* possesses significant neuroprotective effects against H_2O_2 toxicity by suppressing cell apoptosis and encouraging cellular proliferation. Moreover, *Triphala* inhibited the phosphorylation of the mitogen-activated protein kinase signal pathway and increased the concentration of antioxidant enzymes, such as superoxide dismutase 1 and catalase, against HO-treated SH-SY5Y cells (Ning et al., 2021). Polyphenols obtained from *Itrīfal* have been reported to be effective in cognitive impairment and psychiatric disorders by regulating 5-HT and brain-derived neurotrophic factor, antioxidant-related signaling pathways, and gut microbiota (Wang et al., 2023). It has been revealed that the three important ingredients of *Itrīfal*, namely *E. officinalis*, *T. chebula*, and *T. bellirica*, play a pivotal role in managing the functions of the immune and endocrine systems of the body. Studies have reported that *Itrīfal* notably produces immune system stimulation over cytotoxic T cells. The humoral and cell-mediated immune response, complement system activity, and phytohaemagglutinin-induced T-lymphocyte proliferation were also found to be suppressed after administration of three myrobalan fruits. The levels of antioxidant enzymes, T and B lymphocytes, glutathione (GSH), melatonin in the pineal gland, IL-2, IL-10, and TNF were found to be increased after administering an alcohol extract of *T. chebula* (Ahmed et al., 2021).

Scientific studies carried out on some formulations of *Itrīfal* used in Unani medicine have revealed an impressive role in preventing and managing neurological diseases. A study has reported that the different dose levels of *Itrīfal Muqawwī Dimāgh* significantly reduce the climbing ability and oxidative stress level and surge the tyrosine hydroxylase activity in Parkinson's-induced Drosophila flies (Siddique et al., 2021). The *in vitro* reports of *Itrīfal Kishnīzī* have revealed that this preparation remarkably possesses anti-depressant and anti-oxidant activities in a dose-dependent manner (Koneru et al., 2010; Koneru et al., 2011). The aqueous extract obtained from *Itrīfal Aftīmūn* as standalone and as an adjuvant with imatinib has been reported to produce notable antitumor effects against chronic myeloid leukemia cell-lines (K562 and KU812), which is due to the presence of catechin, and caffeic acid in the extract (Gupta et al., 2022). *Itrīfal Saghīr* has been reported to produce a significant anti-obesity effect as compared to the placebo control in a randomized, double-blind, placebo-controlled clinical trial (Kamali et al., 2012). Another formulation, namely *Itrīfal Hakim Ali* has been reported to be clinically significant in decreasing itching, hyperpigmentation, hypopigmentation, and scaling in patients with pityriasis versicolor (Ismail et al., 2022). *Itrīfal Mulayyan* has produced promising antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans*, and *Saccharomyces cerevisiae* (Devi et al., 2011). *Itrīfal Ustukhuddus* significantly produced antihistaminic effects in patients with allergic rhinitis (Hussain et al., 2003). *Itrīfal Shahtra* has been found to be effective in patients with chronic plaque psoriasis (Khatoon et al., 2022).

3.8. Scientific ethnopharmacological evaluation of important ingredients of Itrīfal in brain behavior, cognitive dysfunctions, neurological deficits, psychiatric disorders, and immunocompromised states

3.8.1. Emblica officinalis

The cerebral and neural inflammatory diseases including, Parkinson's disease, Alzheimer's disease, and dementia caused by viruses are produced due to alterations in the complementary pathways. Several biologically active compounds isolated from various plants have been reported to inhibit complementary pathways and oxidative stress in such diseases. A study has confirmed that the administration of *Emblica officinalis* at a dose of 200 mg/ kg for 60 days promisingly decreased acetylcholinesterase and gamma secretase activities and amyloid precursor protein levels in an AlCl3-induced Alzheimer's disease model in rats (Variya. et al., 2016). Some other studies revealed that the methanolic extract prepared from the fruits of *E. officinalis* significantly inhibited AchE in Alzheimer's disease (Saini et al., 2022).The hydro-alcoholic extract of *E. officinalis* promisingly enhanced cerebral cognitive functions via increasing TNF- α levels in the brain tissues (Gaire and Subedi, 2014). Similarly, the hydro-alcoholic extract obtained from *E. officinalis* at 700 mg/kg has been reported to be effective in reducing kainic acid-induced seizures, cognitive impairment, and excessive oxidation in rats' brains. These pharmacological activities are attributed to the presence of bioactive compounds like gallic acid, ellagic acid, emblicanins A & B, corilagin, furosin, and geraniin in Phyllanthus fruit (Golechha et al., 2011). Ellagic acid is a polyphenolic compound present in many plants, including three myrobalan fruits, and has exhibited noteworthy neuroprotective effects through its free-radical scavenging property, ion chelation activity, mitigation of abnormal mitochondrial function, and improvement in the normal functions of various signaling pathways in the nervous system (Gupta et al., 2021a). The fruit of *E. officinalis* has been reported to suppress degeneration in nerve cells in fly models of Alzheimer's disease and Huntington's disease (Gregory et al., 2021). The ethanolic extract of *E. officinals* markedly increased the number of live cells and the function of the mitochondrial membrane with decreased apoptosis and oxidative stress, down-regulated VEGF, and up-regulated PGC-1αagainst the human retinal pigment epithelial age-related macular degeneration transmitochondrial cybrid cell model, thus suggesting the cytoprotective potential of the extract (Nashine et al., 2019). The water extract of *E. officinalis* has been found to have promising antidepressant activity via suppressing MAO-A and GABA pathways (Dhingra et al., 2012). *E. officinalis* also showed significant immunomodulatory and cytoprotective effects in chromium-induced free radical production on lymphocytes (Ram et al., 2002). The remarkable memory-enhancing activity of the powder of *E. officinalis* fruit has been established in fluoride-intoxicated rats (Shalini and Sharma, 2015).

3.8.2. Terminalia bellirica

The methanolic extract prepared from the fruits of *E. officinalis*, *T. chebula*, and *T. bellirica* significantly inhibited acetylcholinesterase enzyme activity in an *in-vitro* model of Alzheimer's disease. Such activity is attributed to the presence of gallic acid, ellagic acid, and other phenolic compounds in the extract (Nag and DE, 2011). Likewise, an *in-vitro* evaluation showed that the methanolic extract of *T. bellirica* exhibited AchE inhibitory effects and potential free radical scavenging activity against reducing power assays and lipid peroxidation assay, whereas the same extract markedly improved the cognitive functions against aluminum chloride and haloperidol-induced amnesia in mice. The study has also suggested that bioactive constituents like gallic acid, β-amyrin, erythrodiol, quercetin, kaempferol, β-sitosterol, stigmasterol,

Table 2
Reported pharmacological activities of various bioactive constituents of different ingredients of *Itrīfal*.

Important ingredients	Part used	Included in *Itrīfal*	Rationale for inclusion on *Itrīfalāt* as per Unani literature	phytoconstituents responsible for pharmacological activities	Pharmacological activities with possible mechanism of actions reported in scientific studies
Emblica officinalis	Dried fruit	*Itrīfal Ustukhuddus*, *Itrīfal Saghīr*, *Itrīfal Kishnīzī*, *Itrīfal Kabīr*, *Itrīfal Zamani*, *Itrīfal Aftīmūn*, *Itrīfal Kishmishī*, *Itrīfal Sanā*, *Itrīfal Zabīb*, *Itrīfal Muqawwī Dimāgh*, *Itrīfal Mulayyin*, *Itrīfal Sanāī*, *Itrīfal M'āmūl* (Anonymous, 2006b; Anonymous., 2006a, 2006b, 2007; Kabeeruddin, 2006)	Cerebral tonic, memory enhancer, useful in headache, gastroprotective (Anonymous., 2007 a), expel melancholic morbid humor, resolvent, demulcent, nervine tonic (Khan, M., A., 2012)	Gallic acid, chebulic acid, chebulinic acid, chebulagic acid, amlic acid, methyl gallate, geranin, corilagin, quercetin, kaempferol, phyllantine, phyllantidine, emblicanin A & B, pedunculagin (Ahmed et al., 2021)	Antioxidant, antidepressant, anti-inflammatory, immunomodulatory, hepatoprotective (Ahmed et al., 2021), anti-atherosclerotic, neuroprotective, cardioprotective, memory enhancing, reducing signs and symptoms of Alzheimer's disease and Parkinson's disease, anti-aging, anti-stress, nootropic (Variya. et al., 2016), immunomodulatory through increasing hemagglutination antibody titer, leukocytes count, cytoprotection, and suppressed apoptosis and DNA fragmentation (Saini et al., 2022)
Terminalia chebula	Dried fruits of different stages (immature, partially mature, mature)	*Itrīfal Ustukhuddus*, *Itrīfal Saghīr*, *Itrīfal Kishnīzī*, *Itrīfal Kabīr*, *Itrīfal Zamani*, *Itrīfal Aftīmūn*, *Itrīfal Kishmishī*, *Itrīfal Sanā*, *Itrīfal Zabīb*, *Itrīfal Muqawwī Dimāgh*, *Itrīfal Mulayyin*, *Itrīfal Sanāī*, *Itrīfal M'āmūl*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2006a, 2006b, 2007; Kabeeruddin, 2006)	Cerebral tonic, useful in eye diseases, analgesic, sedative (Anonymous., 2007 a), gastroprotective, memory enhancer, deobstruent, useful in headache, neuroprotective, expel melancholic, bilious and phlematic morbid humor from brain (Khan, 2018)	Gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, terchebulin, 1,2,3,4,6-penta-O-galloyl-b-D-glucose, casuarinin, chebulanin (Ahmed et al., 2021), ascorbic acid, terflavin A, ellagic acid, ethyl gallate, methyl gallate, eugenol, caffeic acid, rutin, quercetin, luteolin, isoquercetin, tannic acid (Nigam et al., 2020)	Free radical scavenging activity, immunomodulatory activity through deceasing IFN- -γ, and IL−2 and increasing IL−10, anti-aging, cardioprotective (Ahmed et al., 2021), Acetylcholinesterase and butrylcholinesterase inhibitory activity, neuroprotective activity against pheochromocytoma (PC12) cell line, nootropic activity in mice model, reoxygenation of ischemic brain cells, neuroprotective activity through autophagy-induction on human neuroblastoma cell lines (Nigam et al., 2020), anticonvulsant against maximal electric shock and pentylenetetrazole-induced seizures, improved cognitive behaviour (Bulbul et al., 2022)
Terminalia bellirica	Dried fruit	*Itrīfal Ustukhuddus*, *Itrīfal Saghīr*, *Itrīfal Kishnīzī*, *Itrīfal Kabīr*, *Itrīfal Zamani*, *Itrīfal Aftīmūn*, *Itrīfal Kishmishī*, *Itrīfal Sanā*, *Itrīfal Zabīb*, *Itrīfal Muqawwī Dimāgh*, *Itrīfal Mulayyin*, *Itrīfal Sanāī*, *Itrīfal M'āmūl*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2006a, 2006b, 2007; Ghani, 2019; Kabeeruddin, 2006)	Cerebral tonic, eye tonic, gastroprotective (Anonymous., 2007 a; Khan, 2013), demulcent, astringent, expel bilious and melancholic morbid humors(Khan, 2013)	Gallic acid, ellagic acid, termilignan, bellericanin, thannilignan, anolignan B, ethyl gallate, gallolyl glucose, chebulagic acid, phyllemblin, β-sitosterol rhamnose (Nigam et al., 2020), corilagin, galloylpunicalagin, digalloyl-hexahydroxydiphenoyl-hexoside, lignans, bellaric, (Sobeh et al., 2019)	Free radical scavenging activity against DPPH and ABTS models, antifibrotic activity (Chen et al., 2019), hepatocellular antioxidants, hepatoprotective against CCl4-induced hepatotoxicity (Gupta et al., 2020) immunomodulatory activity through reducing asparate aminotransferase, serum alanine aminotransferase, s. alkaline phosphatase, lipid peroxidation, IFN- -γ, and IL−2 biomarkers (Ahmed et al., 2021), increases antioxidant enzyme gene expression (Tanaka et al., 2018), antidepressant effects through interaction with adrenergic, dopaminergic, and serotonergic systems (Dhingra and Valecha, 2007)
Lavandula stoechas	Whole plant	*Itrīfal Ustukhuddus*, *Itrīfal Aftīmūn*, *Itrīfal Zabīb*, *Itrīfal Muqawwī Dimāgh*, *Itrīfal Sanāī*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2006a, 2006b, 2007; Ghani, 2019; Kabeeruddin, 2006)	Resolvent, demulcent, detergent, deobstruent, tonic for vital organs, expel phlegmatic and melancholic morbid humors from brain, neuroprotective, memory enhancer, sedative, analgesic (Khan, 2012)	α-tocopherol, phenethylamine(Mushtaq et al., 2021), 1,8-cineole, lavandulol, necrodane derivatives (Arantes et al., 2016), linalool, linalyl acetate(Cavanagh et al., 2002), ursolic acid (Aydin et al., 2023), pulegone, menthol, menthone, fenchone,β-terpineol, β-pinene(Goren et al., 2002)	Stabilizes memory by augmenting neurotransmission and through antioxidant potential (Mushtaq et al., 2018), improved retention behavior and enhanced memory through increasing choline acetyltransferase, catalase, superoxide dismutase, and glutathione levels in the brain (Mushtaq et al., 2021), antioxidant capacity through inhibiting lipid peroxidation (Arantes et al., 2016), sedative, improving sleep, anxiolytic, local anaesthetic activity through blockade of Na^{-}or $Ca2^{+}$(Cavanagh et al., 2002)

(*continued on next page*)

Table 2 (*continued*)

Important ingredients	Part used	Included in *Itrīfal*	Rationale for inclusion on *Itrīfalāt* as per Unani literature	phytoconstituents responsible for pharmacological activities	Pharmacological activities with possible mechanism of actions reported in scientific studies
Cuscuta reflexa	Whole plant	*Itrīfal Aftīmūn*, *Itrīfal Hakim Alwi Khani*, *Itrīfal Ustukhuddus* (Anonymous., 2006 a; Anonymous., 2007; Ghani, 2019)	Expel phlegmatic and melancholic morbid humors from brain, resolvent, deobstruent (Anonymous., 2007 b), sedative, demulcent ((Khan, 2012))	Cuscutarosides A & B (2), 7β-methoxy-β- sitosterol 3-O-β-glucopyranoside(Tin Thu et al., 2020), 30, 40 -dimethoxy−1-phenyl−1a, 2-ethanediol, tridecanyl palmitate, palmitic acid, n-pentatriacontane, n-triacont−21, 27-dien−1-ol, kaempherol, chlorogenic acid, 5,7-dimethoxyapigenin, quercitin (Nooreen et al., 2019)	*In vitro* thrombolytic, antioxidant, and membrane stabilizing activities (Azad et al., 2018), antimicrobial (Nooreen et al., 2019), improved sleep through blockade of dopamine receptors and enhancement of GABAergic neurotransmission, reduced locomotor activity via increased catecholamines in brain, anxiolytic and hypnotic effects due to increased serotonin level (Pal et al., 2003)
Rosa damascena	Flowers	*Itrīfal Zamani*, *Itrīfal Aftīmūn*, *Itrīfal Sanā*, *Itrīfal M'āmūl*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2006 a; Anonymous., 2007; Ghani, 2019; Kabeeruddin, 2006)	Neuroprotective, cardioprotective, gastroprotective, sedative, analgesic, purgative (Anonymous., 2007 b)	Furfural, geraniol, citronellol, quinic acid (Beigom Hejaziyan et al., 2023), quercetin(Esfandiary et al., 2014), gallic acid, rutin, myricetin, quercitrin, kaempferol (Esfandiary et al., 2015), eugenol, quercetin−3-O-glucoside, kaempferol−3-O-rhamnoside, kaempferol-3-O-arabinoside (Boskabady et al., 2011)	Regulated AchE and increased catalase and glutathione in Alzheimer's model (Beigom Hejaziyan et al., 2023), improved memory through neurogenesis and synaptogenesis by increasing gene expressions like BDNF, NGF, CREB, and EGR−1 (Esfandiary et al., 2014), improved cognitive behavior through free radical scavenging and releasing neurotransmitters (Esfandiary et al., 2015), anticonvulsant against PTZ-induced seizures (Homayoun et al., 2015)[by enhancing benzodiazepines on GABA receptors, antioxidant against DPPH model, ant-aging in Drosophila model (Boskabady et al., 2011), CNS depressant in Alzheimer's disease, hypnotic effect through benzodiazepines receptors (Akram et al., 2019)
Coriandrum sativum	Seed/ Fruit	*Itrīfal Kishnīzī*, *Itrīfal Zamani*, *Itrīfal Kishmishī*, *Itrīfal Muqawwī Dimāgh*, *Itrīfal Sanāī*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2006 a; Anonymous., 2007; Ghani, 2019; Kabeeruddin, 2006; Anonymous., 2008)	Sedative, resolvent, cardioprotective, neuroprotective, gastroprotective, useful in headache (Anonymous., 2007 a), tranquilizer, hypnotic (Khan, 2018)	Monoterpene linalool (Gaston et al., 2016), α-pinene, Y-terpinene, geranyl acetate, camphor, geraniol (Hosseinzadeh et al., 2014), α-thujene, sabinene, β-pinene, myrcene, p-vymene, limonene, z-β-ocimene, y-ter-penin, terpinolene, camphor, citronellal, trpinene−4-ol, and decanal (Mahendra and Bisht, 2011), ferulic acid, gallic acid, caffeic acid, salicylic acid, esculin, esculetin, scopoletin, 4-hydroxycoumarin, umbelliferone, hyperoside, rutin, hesperidin, vicenin, diosmin, luteolin, apigenin, orientine, dihydroquercetin, catechin, arbutin (Jing-Na, et al., 2019)	Anxiolytic and sedative (Gaston et al., 2016), ameliorative erects on memory impairment in SAMP8 mice by increasing NF-L mRNA and decreasing nNOS mRNA in the frontal lobe of the brain(Mima et al., 2020), immunomodulatory effects through increasing immunoglobulin G and M (Hosseinzadeh et al., 2014) [, anti-anxiety potential via GABA receptors (Mahendra and Bisht, 2011), regulated proinflammatory cytokines in brain tissues and effective in Parkinson's disease(Koppula et al., 2021), antioxidant through inhibiting DPPH radicals (Singh et al., 2015)]
Viola odorata	Flowers	*Itrīfal Zamani*, *Itrīfal Sanā*, *Itrīfal Muqawwī Dimāgh*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2006 a; Anonymous., 2007; Ghani, 2019; Kabeeruddin, 2006)	Laxative, resolvent, expel phlegmatic and bilious morbid humors(Anonymous., 2007 c; Khan, 2013), purgative, sedative, anxiolytic, tranquilizer, hypnotic (Khan, 2013)	Rutin (Huang et al., 2022) [, cyclotides (Dayani et al., 2022), 5,7-Dihydroxy−3,6-dimethoxyflavone, 5,7,4′-trihydroxy−3′,5'dimethoxyflavone, 5,7,4′-trihydroxy−3′-methoxyflavone(Karim et al., 2018)	Sedative and anti-anxiety effects through activation of GABA receptors (Huang et al., 2022), improved cognitive behavior via increasing oxidative stress biomarkers and neurotransmitters and decreasing pro-inflammatory markers(Saleem et al., 2021), neuroprotective by activating intracellular pathways and decreasing NF-κB and VCAM−1 expression (Karimifar et al., 2022), immunomodulatory by reducing inflammation and demyelination (Dayani et al., 2022), antidepressant mediated through serotonergic system (Karim et al., 2018), anti-migraine

(*continued on next page*)

Table 2 (*continued*)

Important ingredients	Part used	Included in *Itrīfal*	Rationale for inclusion on *Itrīfalāt* as per Unani literature	phytoconstituents responsible for pharmacological activities	Pharmacological activities with possible mechanism of actions reported in scientific studies
Polypodium vulgare	Rhizome	*Itrīfal Aftīmūn*, *Itrīfal Sanāī*, *Itrīfal Hakim Alwi Khani* (Anonymous., 2007; Ghani, 2019; Kabeeruddin, 2006;)	Expel phlegmatic and melancholic morbid humors (Anonymous., 2007 c; Khan, 2013), exhilarant, cardioprotective (Khan, 2013)	Shikimic acid, caffeoylquinic acid, epicatechin, catechin, gallic acid, rutin(Farras et al., 2021),ecdysteroids(Reixach et al., 1997)	CNS depressant and beta-adrenoceptor agonistic effects (Mannan et al., 1989), antioxidant against 3T3 and HaCaT cell lines (Farras et al., 2021), restore normal intracellular function (Reixach et al., 1997), cholinesterase inhibitory activity in Alzheimer's disease (Saeedi et al., 2017)

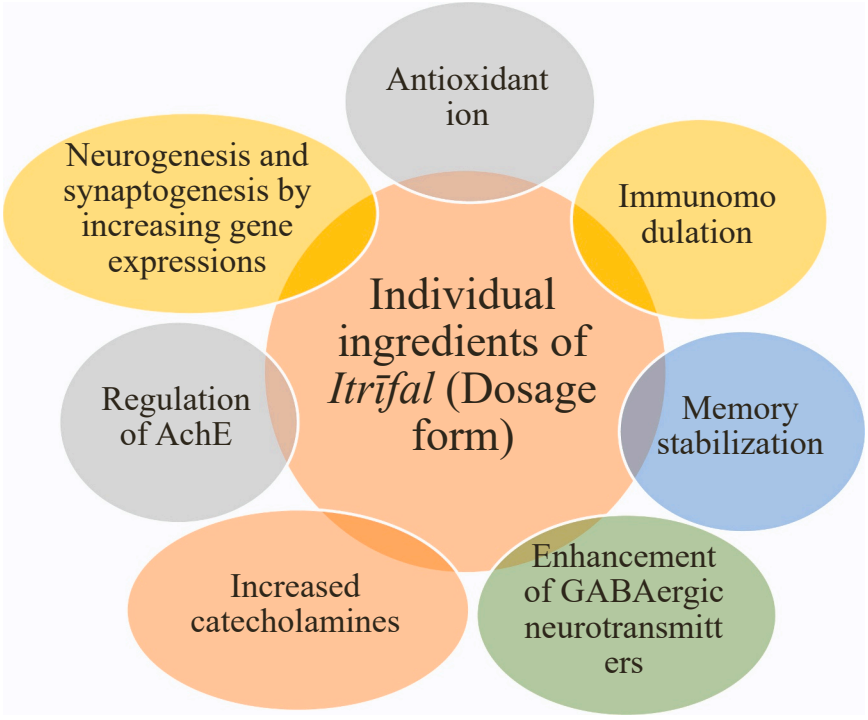

Fig. 2. Mechanism of action of individual ingredients of *Itrīfal* (Dosage form).

lutein, zeaxanthin, and tocopherols are responsible for producing neuroprotective activities (Reddy et al., 2020). The improved learning ability has been observed in mice treated with an aqueous extract of *T. bellirica* (Singh et al., 2021). The ethyl acetate fraction, mainly gallic acid, has been reported to possess extraordinarily high free radical scavenging capacity and modulate gene expression, thereby showed potent anti-fibrotic and proapoptotic activities (Chen et al., 2019) The oral administration of water and ethanolic extracts of *T. bellirica* to mice favourably decreased the immobility time, as observed in the forced swim test and tail suspension test. The anti-depressant activity of both extracts has been elicited through adrenergic, dopaminergic, and serotonergic systems (Dhingra and Valecha, 2007).

3.8.3. *Terminalia chebula*

Pathological studies have described that neuronal inflammation, excessive oxidative stress, and reduced acetylcholine levels in the brain play key roles in producing cognitive dysfunction in patients with Alzheimer's disease. Further scientific investigations have revealed that several phytoconstituents present in the fruit of *T. chebula*, like gallic acid, ellagic acid, chebulagic acid, ellagitannins, tannic acid, and gallotannin, can potentially inhibited the release of proinflammatory neurotransmitters, free radicals, and acetylcholinesterase enzyme (Afshari et al., 2016). Amongst them, chebulagic acid derivatives, including chebulin, have been considered as the most potent ACE-peptide (Sornwatana et al., 2015). The ethanolic extract of *T. chebula* fruit has been reported to possess significant anti-amnesia effects against scopolamine-induced murine models of memory deficit. The study also revealed that it significantly improved cognitive dysfunctions via reducing free radicals, including ROS, NO, and MDA, and decreasing AChE while increasing acetylcholine in the hippocampal tissues of the brain in mice (Min-Soo et al., 2018). Another study demonstrated that the tannin-rich extract of *T. chebula* fruit significantly attenuates GABA antagonist-induced anxiety-like behaviour through increasing locomotor activity and down-regulating serum cholesterol levels like 5-HT, DA, and NE. The gene expressions, including BDNF, CREB, $GABA_A$, and $5\text{-}HT_{1A}$, were also found to be up-regulated in mice. Hence, these findings suggest that *T. chebula* fruit may be used as a natural therapy in the treatment of neurodegenerative diseases(Chandrasekhar et al., 2018). The polyphenolic compounds isolated from the ethyl acetate and n-butanol extracts of *T. chebula* showed marked cerebral and neuronal protective potentials via enhancing antioxidant enzyme activities and augmenting nucleus transportation of nuclear

factor erythroid 2-related factor 2 and expressions of antioxidant proteins, with a concurrent decrease in cell apoptosis and reactive oxygen species levels against cerebral ischemia-reperfusion injury in mice (Lin et al., 2022). Another study has confirmed that the ellagic acid identified in the methanolic extract of *T. chebula* potentially protected the damage of PC12 cells (Yuh-Chiang et al., 2017). Two phytoconstituents, namely punicalagin and geraniin, isolated from the aqueous extract of *T. chebula* fruit, have been reported to produce significant anti-apoptotic and autophagy activation potential against death receptor-mediated apoptosis (Lee et al., 2016). The cold-water extract obtained from *T. chebula* gall showed promising free radical scavenging potential against the DPPH model, a maximum stimulation index was observed on normal human fibroblast proliferation and MMP-2 inhibition activity on fibroblast, which indicated its usefulness in longevity (Manosroi et al., 2010). The remarkable anxiolytic and anti-depressant activities of the ethanolic extract of *T. chebula* fruit have been detected in mice (Mani et al., 2021).

3.8.4. *Lavandula stoechas*

The progressive degeneration in the neuronal cells, myeline sheath, and other structures of the brain causes short-term memory loss, mood swing, speech disorientation, social withdrawals, and altered behaviour patterns. A study has reported that the methanolic extract prepared from the arial parts of *L. stoechas* exhibited significant memory-stabilizing activity, which was evident with a reduction in transfer latencies, an increment in the inflexion ratio, a reduction brain AchE and MDA levels, and increased SOD, GSH, and CAT levels in scopolamine-induced memory loss in mice (Mushtaq et al., 2018). Another investigation revealed that α-tocopherol and phenethylamine present in the aqueous extract of *L. stoechas* are responsible for enhancing memory via improved neurobehavior and cholinergic neurotransmission (Mushtaq et al., 2021). Monoterpenes such as 1,8-cineole, lavandulol, and necrodol derivatives and terpenoids such as γ-terpinene and terpinolene obtained from the lavender essential oil have been reported to produce highly significant anti-oxidant functions against DPPH and lipid peroxidation (Arantes et al., 2016). Some studies have suggested that the phytoconstituents like linalool and linalyl acetate present in *L. stoechas* produce sedative and hypnotic effects by enhancing the activity of GABA in the amygdala. Aromatherapy produces psychological and physical effects due to the odour and volatile constituents. A study revealed that aromatherapy with lavender oil is responsible for increasing the speed and accuracy of mathematical calculations. Other studies have reported that aromatherapy with lavender oil significantly reduced mental stress and anxiety and improved psychological behaviours in patients (Cavanagh et al., 2002).

3.8.5. *Cuscuta reflexa*

Anxiety and depression associated with chronic pain are important clinical manifestations of most neuropsychiatric disorders. The discharge of pro-inflammatory chemical mediators and neurotransmitters, especially serotonin and nor-epinephrine, plays a significant role in the development of anxiety and progressive depressive illnesses. Other neurobiological mechanisms involved in such diseases are disturbances in the GABA-ergic, and glutamatergic pathways of the central nervous system. A study has reported that the methanolic extract of *C. reflexa* leaves significantly modulates the synthesis of neurotransmitters and cerebral receptors. Further, it was confirmed that the same test substance produced promising anti-depressant activity against tail suspension test and force swimming test in mice. The docking study has further confirmed that the exerted response of the methanolic extract of *C. reflexa* leaves is due to the presence of phytoconstituents like quercetin, kaempferol, myricetin, astragalin, linoleic acid, coumarin, ß-sitosterol, luteolin,α-amyrin, sesamin, and isorhamnetol (Adnan et al., 2020). Another study has confirmed that the petroleum ether extract of *C. reflexa* stem markedly increased sleeping time and improved general behaviour profile through modifying GABA-ergic transmission in mice. Additionally, the biochemical investigation revealed that neurotransmitters like dopamine, epinephrine, and nor-epinephrine were found to be raised in the serum of extract-administered mice (Pal et al., 2003). The acetone extract prepared from *C. reflexa* has been reported to produce potent anti-oxidant activity on the DPPH assay and anti-tyrosinase activity, which might be due to the presence of phenolic compounds, such as rutin, quercetin, and vanillic acid in the extract (Tanruean et al., 2017). The marked immunomodulatory and free radical scavenging activities of *C. reflexa* extracts have been observed on DPPH and T-cell lymphocyte models, respectively(Singh et al., 2022).

3.8.6. *Rosa damascena*

Several plant-origin drugs, including *R. damascena* have been, proven to produce an optimum level of protective and therapeutic effects in many neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, dementia, etc. A study revealed that the methanolic extract obtained from *R. damascena* markedly increased spatial memory and long-term memory and reversed cognitive impairment attributed to the presence of flavoinoids and polyphenolic compounds in the extract in an amyloid-β-induced Alzheimer`s disease model in rats (Esfandiary et al., 2015).In support of these pre-clinical findings, a clinical trial has confirmed that *R. damascena* extract capsules along with donepezil significantly improved cognitive functions and psychological behaviours as compared to donepezil as an adjuvant with placebo capsules in 40 patients suffering from dementia (Esfandiary et al., 2018). The hydro-alcoholic extract of *R. damascena* showed significant anti-convulsant and neuroprotective potential, as evident by the decreased production of dark nerve cells in various regions of hippocampus in a pentylenetetrazole-induced epileptic model of rats (Homayoun et al., 2015). The oral administration of the extract of *R. damascena*for one month in a rat model of Alzheimer's disease markedly improved hippocampal-dependent learning and memory by increasing the growth of supportive neurons, hippocampal volume, and repair of synapses in the brain. Flavonoids present in *R. damascena* have been reported to protect neurons from toxins and other inflammatory mediators and improve learning, memory, and cognitive functions by inhibiting apoptosis and encouraging neuronal survival, neurogenesis, angiogenesis, synaptic plasticity, neuronal morphology, and cerebrovascular blood flow (Esfandiary et al., 2014). The aqueous extract of *R. damascena* has shown promising neuroprotective properties by increasing spatial memory, catalase, and glutathione levels, reducing MDA levels, and modulating AchE activity against aluminium chloride-induced neurotoxicity in rats (Beigom Hejaziyan et al., (2023). Another piece of data supports that *R. damascena* extracts enhance memory and protects against neurodegeneration through inducing neurogenesis and synaptic plasticity (Esfandiary et al., 2014). A randomized controlled clinical trial revealed that aromatherapy with rose oil remarkably reduced the anxiety level and improved the quality of sleep in personnel working in operating room (Mahdood et al., 2022). Similarly, a meta-analysis report revealed that the oral administration and aromatherapy with *R. damascena* significantly reduced the activity of the sympathetic nervous system, increased production of nerve growth factors through the mechanisms of neurogenesis and synaptic plasticity, decreased prolactin, and increased estradiol, noradrenaline, and progesterone levels in the serum (Mohamadi et al., 2022).

3.8.7. *Coriandrum sativum*

The sedative property of the essential oil obtained from *C. sativum* and its monoterpene component, linalool,was evaluated in chicks. The results exhibited that direct administration of both test drugs in the brain through injection produced similar sedative activity as diazepam (Gaston et al., 2016). Another study has reported that the oral administration of *C. sativum* seed extract for 3 months significantly improved the age-related memory of senescene-stimulated SAMP8 mice (Mima et al., 2020). The extract prepared from the fruit of *C. sativum* significantly reduced nitric oxide, nitric oxide synthase, tumour necrosis

factor-α, interleukin-6, and cyclooxygenase-2 levels and inhibited kappa-beta activation and 1_kB-α phosphorylation in a lipopolysaccharide-induced BV-2 microglia-mediated neuroinflammation model in vitro. Further, the *in vivo* study promisingly improved behaviour, cognitive, and locomotor functions and restored brain-oxidative enzymes in a 1-methyl-4 phenyl-1, 2, 3, 6-tetrahy-dropyridine-induced Parkinson's disease model of mouse (Koppula et al., 2021). The extract obtained from the fruit of *C. sativum* has been reported to reduce insulin, oestrogen, FSH, LH, SOD, and CAT levels and to increase NO and MDA levels significantly as compared to the control in the STZ-administered diabetic gonadal dysfunction model in female rats and their offsprings, which showed remarkable immunomodulatory activity (Attaallah et al., 2023). The hydro-alcoholic extract of *C. sativus* seed has shown promising anti-oxidative effects in the lead-intoxicated cerebral regions of rats (Velaga et al., 2014).Moreover, some studies have reported that the flavonoids isolated from the aqueous extract of the seeds of *C. sativum* markedly suppress the injury caused by excessive oxidation after administering lead in animal models (Sobhani et al., 2022).

3.8.8. *Viola odorata*

A study has reported that *V. odorata* extract significantly produced neuroprotective activity against SDG-induced cell death through its antioxidant properties (Mousavi et al., 2016) Another study has reported the promising neuroprotection activity of *V. odorata* extracts in a cerebral artery occlusion model via decreasing the expression of *NF-κB* and *VCAM-1* (Karimifar et al., 2022). Many systemic studies have suggested that *V. odorata* extracts remarkably increased sleeping time in patients with chronic insomnia (Huang et al., 2022). The methanolic extract obtained from *V. odorata* has been reported to improve cognitive dysfunction, as evident by reducing oxidative stress, inflammatory cytokines, and AChE levels (Saleem et al., 2021).

3.8.9. *Polypodium vulgare*

The methanolic extract of *P. vulgare*has shown promising antioxidant activity against 3T3 and HaCaT cell lines due to the presence of polyphenolic compounds (Farras et al., 2021). The water extract prepared from the roots of *P. vulgare* has shown significant CNS depressant activity, as evident with a reduction in motor functions and body temperature, prolongation of the pentobarbitone-administered sleeping time, and augmented reaction time to pain stimuli. The test drug also reduced seizures in supramaximal electroshock and pentylenetetrazol-stimulated epileptic models of animals. The positive inotropic and chronotropic properties of the methanolic extract of *P. vulgare* were also observed in the hearts of frogs, which conformedto itsβ-adrenoceptor agonistic effect (Mannan et al., 1989).The *in vitro* anti-cholinesterase activity of *P. vulgare* rhizome has also been reported (Saeedi et al., 2017).

4. Discussion

Itrīfal, a semisolid dosage form, is used for the prevention and treatment of several cerebral and other systemic ailments of the body, such as cerebral weakness, paralysis, epilepsy, dementia, melancholia, psychosis, mixed anxiety depressive disorders, headache, vertigo, chronic rhino-sinusitis, constipation, etc (Anonymous., 2006a, 2006b, 2007, 2008). Ancient Unani physicians like Ibn Sina, Jurjani (Jurjani, 2010), and Haruni (Al-Haruni, 2018), and renowned Indian Unani physicians of the 17th and 18th centuries like Arzani, Shareef Khan, and Azam Khan have described this important dosage forms in their masterpieces, which suggested the rationale use of *Itrīfal* since olden days till date. This important dosage form was introduced with the wisdom for the elimination or neutralization of oxidized all four humors, especially black bile from the body, which is produced due to unwanted combustion. The review of current research studies discloses that oxidative stress, generation of reactive oxygen species, and cerebrovascular congestion are contributing key roles in the pathogenesis of many cerebral, neurological, and psychiatric disorders, including stroke, Parkinson's disease, Alzheimer's disease, depression, melancholia, insomnia, mixed anxiety depressive disorders, dementia, etc., which validates the age-old concept of *ihtirāq* discussed in Unani medicine (Kausar et al., 2021). The Unani pharmacopoeia and classical texts revealed several formulations of this dosage form, which contain three myrobalan fruits as chief ingredients and other ingredients of mainly plant origin. *Muqawwī-i-dimāgh* (brain tonic) and *muqawwī-i-a'sāb* (nervine tonic) (Anonymous, 2012) are two commonly preferred terminologies in reference to the drugs used in the prevention and treatment of cerebral, neurological, and psychiatric disorders. The three myrobalan fruits are reported to have *muqawwī-i-dimāgh* (brain tonic) properties in Unani classical literature (Anonymous., 2007a). The results of the present review revealed many interesting facts about the wisdom behind the composition of the formulations of *Itrīfalāt*. *Emblica officinalis*, commonly known as Indian gooseberry, belongs to the Euphorbiaceae family (Krishnaveni and Mirunalini, 2010), is traditionally used to increase longevity and memory and as a nervine and brain tonic (Anonymous., 2007a). Several scientific studies have confirmed that the fruit of *E. officinalis* significantly produces antioxidant, immunomodulatory, memory-enhancing, antidepressant (Ahmed et al., 2021), neuroprotective, anti-aging, nootropic activities, etc., (Variya. et al., 2016) in various diseased models due to the presence of many bioactive secondary metabolites. *Terminalia chebula*, another chief ingredient of *Itrīfal*, belongs to the Combretaceae family and showed a wide range of neuropharmacological activities because of the presence of a diverse range of bioactive constituents, including flavonoids, phenolic compounds, tannins, minerals, etc. It is useful in improving cognitive functions and brain behaviors and preventing neurodegeneration by inhibiting proinflammatory mediators and acetylcholinesterase enzymes, free radical scavenging activity (Nigam et al., 2020), and reoxygenation of ischemic brain tissues in cases of Alzheimer's disease (Afshari et al., 2016), memory deficit (Min-Soo et al., 2018) Parkinson's disease, and other neurodegenerative conditions (Chandrasekhar et al., 2018). The dried fruit of *Terminalia bellirica* is also added as a chief ingredient in the formulations of *Itrīfal*. Phytochemical investigations have reported that it contains ellagic acid, chebulaginicacid, gallo-tannicacid, ethyl gallate, galloyl glucose, arjunolicacid, phenyllemblin, ignans, β-sitosterol, corilagin, etc., as major biologically active constituents (Gupta et al., 2021b). Amongst them, ellagic acid has shown marked neuroprotective ability through its free-radical scavenging activity, induction of many cell signaling pathways, iron chelation, and improvement in mitochondrial functions (Gupta et al., 2021a). *Lavandula stoechas*, belonging to the Lamiaceae family, an important herb, is used as a brain scavenger in Unani medicine for the prevention and treatment of brain stroke, paralysis, epilepsy, melancholia, etc (Ahmed et al., 2016). The neuroprotective, memory-stabilizing, anti--oxidant, sedative, and anxiolytic activities of *L. stoechas* are attributed to the presence of monoterpenes in its volatile oil (Arantes et al., 2016; Ahmed et al., 2016). According to Unani theory, *Cuscuta reflexa* is a potent drug to eliminate phlegmatic and melancholic morbid substances from the brain (Anonymous, 2007 b). The ethanol extract of *C. reflexa* whole plant has shown remarkable thrombolytic, membrane-stabilizing, and anti-oxidant activities in *in vitro* models (Azad et al., 2018). The multifarious therapeutic efficacy of *Rosa damascena* in psychiatric and other neurological diseases is attributed to the presence of glycosides and phenolic compounds (Esfandiary et al., 2018). Contemporary research has proved that the neuroprotective, anxiolytic, anti-oxidant, and anti-convulsant effects of *Coriandrum sativum* are associated with the presence of polyphenolic compounds, coumarins, phytosterols, terpenoids, and fatty acids (Sobhani et al., 2022). The sedative, anxiolytic, tranquilizing, and hypnotic effects of *V. odorata* mentioned in Unani literature (Khan, 2012) have been confirmed by recent scientific studies (Huang et al., 2022).

Itrīfal is not only considered an old dosage form in the Unani system

of medicine; it is also useful in the prevention and management of cerebral, neurological, autoimmune, and other diseases, as evident from the reports of Unani classical manuscripts and scientific studies. The pharmacological profiles of few compound formulations of *Itrīfal* and nine commonly used ingredients of *Itrīfal* were explored scientifically. Excitingly, positive evidence has been found in the correlation of the claims of Unani medicine and contemporary research that most of the therapeutic indications of the formulations of *Itrīfal* in general and their ingredients in particular potentially act in the prevention and treatment of cerebral, neurological, psychiatric, and autoimmune diseases. The limitations of this metanalysis are that the whole preparations of many *Itrīfal* are not scientifically studied yet. Many formulations, such as *Itrīfal Ustukhuddus*, *Itrīfal Saghīr*, *Itrīfal Kabīr*, *Itrīfal Zamani*, *Itrīfal Aftīmūn*, *Itrīfal Kishmishī*, *Itrīfal Sanā*, *Itrīfal Zabīb*, *Itrīfal Mulayyin*, *Itrīfal Sanāī*, *Itrīfal M'āmūl*, *Itrīfal Hakim Alwi Khani*, etc. are indicated for use in the prevention and treatment of various neurological diseases. The phytopharmacological reports have confirmed that various active biological constituents present in different plant-based ingredients of *Itrīfal* potentially beneficial in preventing and treating neurobehavior, neurodegenerative, and immune system-related diseases. In light of the present review, it is therefore, suggested that the therapeutic efficacy and safety of such an important dosage form, in different neurological, psychiatric, and autoimmune disorders like stroke, Parkinson's disease, Alzheimer's disease, depression, melancholia, insomnia, mixed anxiety depressive disorders, dementia, etc. may be scientifically explored in the future.

5. Conclusion

The treatment of cerebral, neurological, psychiatric, and immune system disorders is still a challenge with conventional modern medicine. Nonetheless, phytomedicine plays a pivotal in preventing and treating such diseases. It is evident that oxidative stress and excessive generation of reactive oxygen species in the brain and nerves are associated with several neurological and other body system diseases. A number of formulations of *Itrīfal* described in Unani pharmacopoeias contain a thoughtful mixture of plant-based ingredients, which possess neuroprotective and immunomodulatory effects through diverse mechanisms of action, including inhibition of cholinesterase enzymes and proinflammatory mediators, modulation of neurotransmitters, autophagy-induction, dopaminergic, blockade of Na^{-}or $Ca2^{+}$, enhancement of GABAergic neurotransmission, neurogenesis, synaptogenesis, thrombolytic, membrane-stabilizing activities, etc. The current appraisal revealed that various formulations of *Itrīfal* are traditionally used in the prevention and treatment of cerebrovascular, neurological, and psychiatric diseases. Recent research carried out on a few formulations of this dosage form has confirmed that they significantly reduced oxidative stress and increased memory in cases of Alzheimer's disease. Furthermore, studies have also proved that the important ingredients of this dosage form, such as *E. officinalis*, *T. chebula, T. bellirica, L. stoechas, C. reflexa, R. damascena, C. sativum, V. odorata,* and *P. vulgare*, exerted promising antioxidant, antidepressant, anti-inflammatory, immunomodulatory, memory-enhancing, neuroprotective, anti-ageing, anticonvulsant, anxiolytic, sedative activities, etc. in various models of neurological and cerebral diseases. Phytochemical analysis of the ingredients present in *Itrīfal* has confirmed that the above-mentioned pharmacological activities are associated with the diverse nature of active secondary metabolites. It is therefore concluded that the present review validates the therapeutic claims of *Itrīfal* with respect to its use in the brain and other neurological disorders. The present review generates ample evidence for researchers to carry out further studies on scientific lines for exploring the pharmacological profile, pharmacokinetic studies, safety profile, activity-based explanation of action-mechanism, etc. of different formulations and individual ingredients of *Itrīfal* with reference to neurodegenerative, neurobehavior, psychological, and other neurological diseases. Thus, this important, age-old Unani dosage form may be comprehensively elaborated for the benefit of masses.

CRediT authorship contribution statement

Zaheer Ahmed: Writing – review & editing. **Athar Parvez:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kabiruddin Ahmed:** Writing – review & editing. **Noman Anwar:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Athar Parvez Ansari reports was provided by Central Council for Research in Unani Medicine. Athar Parvez Ansari reports a relationship with Central Council for Research in Unani Medicine that includes:. Athar Parvez Ansari has patent It is a review article (Not applicable) pending to It is review article (Not applicable). No conflict of interest If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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